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Thyroid Nodules and Thyroid Cancer: Surgical Aspects

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Patients with thyroid nodules must be treated selectively because these nodules develop far more frequently than does thyroid cancer. A thorough clinical history, family history and history of radiation, as well as an accurate physical examination, are very important in determining whether surgical treatment is indicated. Thyroid function tests, a radioactive isotope scan, a thyroid echogram and fine-needle biopsy are also useful.

Although there is considerable debate concerning the amount of thyroid tissue that should be removed at operation, the minimal procedure for a "cold," solid thyroid nodule is a total thyroid lobectomy and isthmectomy. This is the treatment of choice for patients with occult papillary thyroid carcinoma. Partial lobectomy is to be discouraged. Near total or total thyroidectomy should be considered for all other patients with differentiated thyroid cancer.

Many factors influence the prognosis of patients with thyroid cancer including age, sex, type of thyroid cancer, invasion, symptoms, lymph node metastasis, metastasis to distant sites, extent of the surgical procedure, and use of radioactive iodine and thyroid hormone. With adequate treatment, the prognosis for differentiated thyroid carcinoma is excellent.

THE OCCURRENCE OF thyroid cancer is increasing, and considerable debate exists over the selection of patients with thyroid nodules for thyroidectomy and how much thyroid tissue should be removed at operation.[1-3] Patients with thyroid nodules must be treated selectively. While about 4 percent of persons in the United States have thyroid nodules, only .004 percent or 40 persons per million have thyroid cancer, and only 6 patients per million die of this disease.[4-6] The variable and generally prolonged course of thyroid cancer, the hormone dependence of many thyroid tumors and the wide spectrum of neoplasms with varying biologic characteristics, make the evaluation and interpretation of various methods of treatment difficult.

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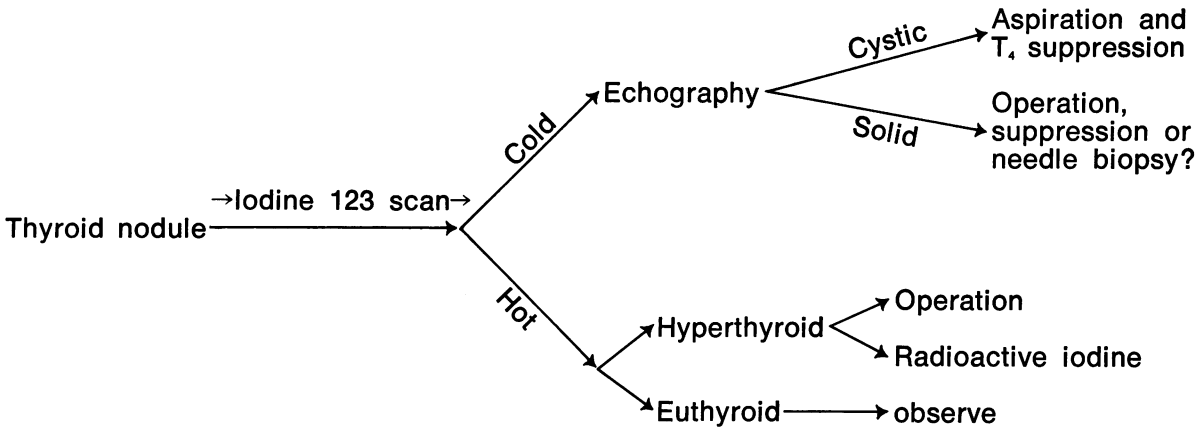
Evaluation of Patients

This paper presents a logical approach to the diagnosis and treatment of patients with nodular goiter. Clearly, the main concern when evaluating a thyroid nodule is whether the nodule is malignant. Observation alone, without surgical intervention, is appropriate in some patients: those with diffusely enlarged goiters or multinodular

ABBREVIATIONS USED IN TEXT
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

goiters without a dominant lesion, with high antithyroid antibody titers, with a family history of benign goiter or with nodules that disappear after treatment with an exogenous thyroid hormone. However, young patients with thyroid nodules, patients with "cold," solid thyroid nodules or nodules that are growing, those who have received radiation therapy, and those with nodules, in whom hoarseness, dysphagia, cervical adenopathy or a hard fixed thyroid mass has occurred, must be considered candidates for operation.[7,8] Thyroid cancer also occurs in patients with multiple endocrine adenomatosis type II or the Sipple syndrome (medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism).

All patients with thyroid nodules should be evaluated for any localized or systemic symptoms, and their thyroid function determined. Virtually all adult patients with a clinically solitary or dominant thyroid nodule should have a radioactive iodine (iodine 123) scan. The scan helps confirm the accuracy of the clinical examination, determines whether the lesion is solitary or multiple and whether it is nonfunctioning ("cold") or functioning ("warm" or "hot"). Multinodular goiters have a lower incidence of thyroid cancer than solitary nodules. Hot nodules detected by radioactive iodine scan are rarely malignant, but may cause hyperthyroidism, whereas cold solitary thyroid nodules have a 20 percent chance of being malignant[7] (Figure 1). A ^{123}I or technetium 99m scan using a gamma (scintillation) camera with a pinhole collimator is also recommended for all patients who have received 6.5 or more rads to the thyroid as children or as young adults, because thyroid nodules may be missed on physical examination. Also, as little as 6.5 rads to the thyroid gland is associated with a sixfold increase in thyroid cancer when compared with siblings who have not undergone radiation therapy. Thyroid



T_4 = thyroxine

Figure 1.—Recommended method of evaluating a patient with a thyroid nodule.

TABLE 1.—*Thyroid Lesions After Irradiation**

Area or Type of Treatment	*Estimated Dose to Thyroid (Rads)*	*Incidence (Percent)*		*Source*
		Nodular Goiter	*Cancer*	
Scalp	6.5	..	0.11	Modan et al[10]
Thymus				
Total group	119	1.8	0.8	Hempelmann et al[11]
Subgroup	399	7.6	5.0	
Neck, chest	807	27.2	5.7	Favus et al[12]
	180-1,500	26.2	6.8	Refetoff et al[13]
Radiation fallout	175(γ) and 700-1,400 (β)	39.6	5.7	Conard et al[14]
^{131}I therapy	±10,000	0.17	0.08	Dobyns et al[15]

*Adapted from Greenspan FS: Radiation exposure and thyroid cancer. JAMA 237:2089-2091, 1977

TABLE 2.—*Diagnostic Radioactive Pharmaceutical Examinations and Estimated Dose to the Adult Thyroid Gland**

Radioactive Pharmaceutical Agent and Type of Examination	*Estimated Dose to Adult Thyroid (Rads)*
^{123}I thyroid scan	2.8
^{123}I thyroid uptake	6.0
^{131}I thyroid uptake	10.5
^{131}I thyroid scan	100-200
^{99m}Tc thyroid scan	0.1

*Adapted from Silverman C, Hoffman DA: Thyroid tumor risk from radiation during childhood. Prevent Med 4:100-105, 1975

cancer has also been reported to occur in 22 of 62 patients (35.5 percent) in whom scans showed abnormalities but physical examinations did not.[9] Multiple radioactive iodine scans are not recommended unless cancer has been discovered.

Table 1 shows the relationship between the dose of radiation administered and the development of thyroid disease. The radiation dose most likely to induce thyroid cancer is approximately 1,500 rads. However, as little as 6.5 rads to the thyroid gland, received during the course of radiation of the scalp for tinea capitis, resulted in a sixfold increase in thyroid cancer: 0.11 percent in treated patients compared with 0.02 percent in untreated siblings. In dose ranges of 400 to 1,500 rads, the incidence of nodular goiter was about 27 percent to 40 percent, whereas the incidence of thyroid cancer varied from 5 percent to 9 percent. With larger doses of thyroid radiation, the incidence of malignant neoplasms seems to decrease but the incidence of hypothyroidism increases.

The amount of radiation that the thyroid receives from the various thyroid scans is summarized in Table 2. The absorbed radiation dose to the thyroid depends on the following: amount administered, type of radioactive isotope, percent uptake, size of thyroid gland, age of subject and route of administration. Thyroid-absorbed doses vary greatly with age—they are lowest in adults (20 years of age and older), progressively higher in children, and in newborns may be more than 20 times the adult dose.

If a thyroid lesion is cold, thyroid echography is recommended. Approximately 15 percent of the cold nodules are cystic, and *cysts* of the thyroid are rarely malignant.[16,17] However, metastatic thyroid cancer in regional nodes is frequently cystic.[18] If the thyroid nodule is cystic by echography, then treatment by aspiration is safe and makes operative removal unnecessary in about 70 percent of patients because the lesion either disappears or dramatically regresses leaving a minimal residual lesion.[18]

Fine-Needle Biopsy

Fine-needle biopsy of solid thyroid nodules also seems valuable in selected patients. Biopsy is not recommended in patients who have previously received radiation treatment because of the multifocal nature of these tumors.[19] Needle biopsy is (1) safe and provides additional diagnostic material, (2) reliable for Hashimoto thyroiditis and undifferentiated thyroid tumors and (3) as accurate as frozen section (approximately 80 percent) for thyroid nodules.[20-22] Needle biopsy also rarely gives false-positive diagnostic information and needle tract implantation is rare.[23] To my knowledge there has been no documented case of local tumor extension in the needle tract following fine-needle (18- to 22-gauge) biopsy. The main limitations of percutaneous needle biopsy include false-negative diagnosis because of incorrect location of sampling[24] and the inability to distinguish between a well-differentiated follicular carcinoma and a highly cellular benign follicular adenoma.[23] As long as the clinician and patient are aware of these limitations and biopsy is viewed as an additional diagnostic aid to the history and to physical and laboratory findings, then percutaneous biopsy is useful for evaluating thyroid nodules. Close cooperation with a competent anatomic pathologist or cytologist is essential for biopsy to be helpful.

Factors Influencing Survival

Factors that influence prognosis in patients with thyroid cancer are age, sex, type of thyroid cancer, size of the tumor, invasion, symptoms, lymph node involvement, metastasis to distant sites, extent of surgical operation, use of radioactive iodine and exogenous thyroid hormone therapy.[3,25-27]

Virtually all studies concerning differentiated thyroid cancer show that patients younger than 7 or older than 40 years of age are more likely to die of this cancer than those between 8 and 39 years.[8] This is in spite of the fact that the recurrence of cancer is more common in younger persons. Women have a greater incidence of thyroid cancer than men, but men have a worse prognosis. Women also have more benign thyroid nodules than men, therefore any given thyroid nodule is more likely to be malignant

in a man than in a woman. Although most forms of thyroid cancer are not symptomatic, those which cause pain, hoarseness, dysphagia or grow rapidly have a more ominous prognosis and usually represent either dedifferentiation to undifferentiated lesions or anaplastic tumors. Large tumors (more than 2.5 cm in size), invasive tumors and those that have metastasized to distant sites also adversely influence survival. Whether or not lymph node metastasis influences survival is controversial.[28-31] Studies from the Lahey Clinic suggest that lymph node metastasis may be beneficial.

Because numerous investigations have shown that microscopic thyroid cancer is present in approximately 75 percent of patients undergoing prophylactic neck dissections (and who had no grossly perceptible lesions),[32-33] I believe that lymph node metastasis indicates the presence of more cancer. At the University of California, San Francisco, when patients with and those without nodal metastasis were matched for age, the presence of nodal metastasis signified a poorer prognosis. It should be mentioned, however, that lymph node metastasis is most common in the young, with as many as 80 percent of children having clinically positive nodes at the time of diagnosis.[34] Only about 20 percent of patients older than 30 years have metastatic disease.[34] Even so, children with nodal metastasis still have an excellent long-term prognosis.[31-34]

Thyroid Pathology

Obviously, the type of thyroid cancer is important in predicting survival. Primary thyroid tumors generally may be separated into benign (adenoma, cyst, localized thyroiditis) and malignant categories, but in some instances the distinction is difficult. The types of adenoma include follicular, embryonal, atypical, Hürthle cell and papillary (although some observers consider all papillary tumors to be a form of carcinoma). The types of malignant tumors are given in Table 3.

For atypical adenomas a minimum of eight satisfactory histologic blocks, including the capsule, should be surveyed to rule out invasion of the capsule. *Occult* papillary carcinomas (1 cm or less in size) have a very favorable prognosis. In fact, if an occult tumor is removed in the course of a thyroidectomy done for another reason, it should be considered as an incidental finding that requires no additional surgical treatment. Occasionally, widespread metastatic lesions may occur with an occult primary carcinoma. When cervical lymph nodes contain metastatic thyroid cancer (lateral aberrant thyroid) and no lesion is palpable in the thyroid gland, the occult papillary cancer is virtually always in the ipsilateral lobe of the thyroid gland. Psammoma bodies are frequently found (60 percent to 70 percent) in papillary thyroid cancer and rarely found in follicular thyroid cancer, but they are of no prognostic significance.[35] Papillary carcinoma, which accounts for about 60 percent to 80 percent of cases of thyroid cancer, has the most favorable prognosis; follicular carcinoma (20 percent to 30 percent) has a slightly poorer prognosis, and undifferentiated or anaplastic carcinoma (1 percent to 5 percent) has a dismal prognosis. Life expectancy in patients with differentiated (papillary, mixed-follicular and follicular) carcinoma is usually compared at 15 years, whereas 80 percent to 90 percent of patients with undifferentiated thyroid carcinoma are dead within a year. Medullary carcinoma has an intermediate prognosis between the differentiated and undifferentiated types (Figure 2).

TABLE 3.—*Malignant Tumors of the Thyroid Gland*

Differentiated carcinoma
Papillary (60%-80%)
Occult
Pure papillary
Mixed papillary-follicular
Follicular (20%-30%)
Encapsulated or slightly invasive
Invasive
Undifferentiated carcinoma (10%-15%)
Anaplastic, squamous cell, spindle cell, giant cell, small cell
Medullary (1%-5%)
Other (1%-5%)
Lymphoma
Fibrosarcoma
Malignant teratoma
Malignant mixed tumors
Metastatic tumors

Extent of Surgical Intervention

There is considerable controversy about the extent of surgical intervention for thyroid cancer. Virtually all clinicians agree, however, that the minimal operation for a solitary thyroid nodule is a thyroid lobectomy and isthmectomy on the side of the nodule.[26,27] If the nodule is situated in the isthmus, resection of the isthmus along with the anterior third of each lobe is usually recommended. If frozen section shows the lesion to be benign then the operation is completed. If

malignant, more tissue should be removed. Factors influencing the amount of thyroid tissue to be removed include (1) type of cancer, (2) involvement of the contralateral lobe, (3) metastasis, (4) experience and prejudice of the surgeon, (5) intelligence and reliability of the patient and (6) history of radiation exposure to head and neck. Obviously, if there is bilateral involvement of the thyroid gland with cancer, a near total thyroidectomy (preserving the posterior lateral capsule on the side of the neck with less tumor) or total thyroidectomy should be done, regardless of whether the tumor is papillary, follicular or medullary. Cutting through gross tumor increases the chance of tumor recurrence and shortens survival.[3,26] The rate of recurrence within the thyroid in these patients ranges from 30 percent to 50 percent.[6]

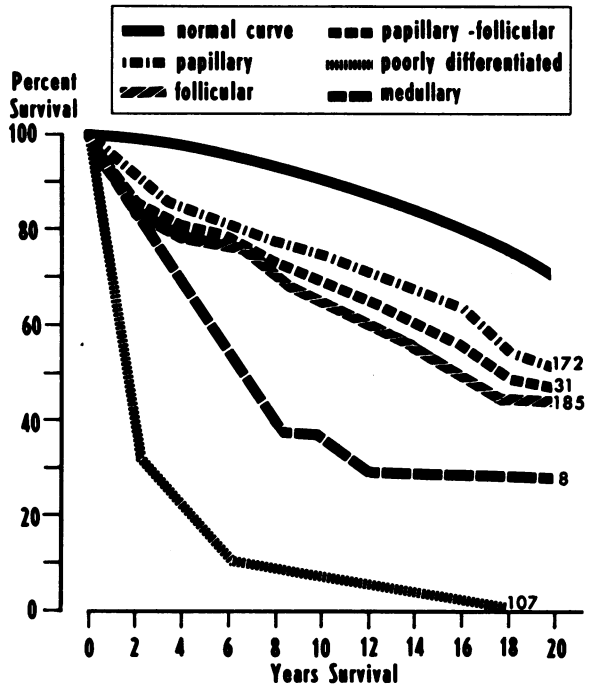


Figure 2.—Survival curves for several types of thyroid cancer. Normal population from interpolation of the Abridged Life Tables. Numbers indicate number of patients. (Data from Buckwalter JA, Thomas CG Jr: Selection of surgical treatment for well differentiated thyroid carcinoma. Ann Surg 176:565-578, Oct 1972.)

TABLE 4.—*Reasons for Total Thyroidectomy*

- As many as 87.5 percent of patients have microscopic cancer in the contralateral lobe.
- In approximately 7 percent to 10 percent of patients recurrent clinical cancer in the remaining lobe develops.
- Half of the patients in whom recurrent thyroid cancer develops die of this disease.
- A fourth to a half of the patients who die of thyroid cancer do so because of unresectable central neck disease.
- The chance of a differentiated thyroid cancer becoming an anaplastic thyroid cancer, which occurs in approximately 3 percent to 5 percent of cases, becomes less likely.
- Follow-up with radioactive iodine scanning is easier to evaluate for disseminated disease.
- Thyroglobulin can be used as a tumor marker for metastatic differentiated thyroid cancer because serum levels should be negligible in patients after total thyroidectomy.

Near total thyroidectomy is the operation done most commonly in the United States for the treatment of papillary carcinoma.[6] Some investigators favor a total or near total thyroidectomy for all papillary, follicular and medullary thyroid cancer except for localized occult cancer, in which the prognosis with lesser procedures is excellent. This approach must be used with some reservation because a lobectomy has been shown to be an acceptable means of treating papillary thyroid cancer grossly confined to one lobe, and offers a prognosis of long-term survival comparable with that of more extensive operations.[26] If the incidence of permanent hypoparathyroidism is higher than 1 percent after total or near total thyroidectomy, then less than a total thyroidectomy should be done. Reasons for total thyroidectomy are listed in Table 4.

Unfortunately, most forms of undifferentiated thyroid cancer are unresectable at time of operation. Therefore, generally the surgical goal is to obtain tissue for histological examination so that radiation therapy can be given.[36]

Neck Dissection

Papillary and some follicular carcinomas spread via the local lymphatic channels. A modified radical neck procedure is recommended in these patients when lymph nodes are clinically involved. Several studies suggest that survival and recurrence rates are similar in patients treated by either a standard radical or a modified radical neck dissection.[6,37] Prophylactic neck dissections are not recommended for papillary and follicular thyroid carcinoma because, despite the fact that tumors may be discovered in about 75 percent of these patients, the tumors recur in only about 10 percent of them. Delay in removal of lymph nodes until they become palpable does not appear to influence survival.[3,38,39] A modified neck dissection using an en bloc procedure is recommended rather than "berry picking" because

whenever a node larger than 3 mm contains thyroid cancer, cancer will always be found in the smaller lymph nodes.[33] During an en bloc dissection, however, the spinal accessory nerve, sternocleidomastoid muscle and internal jugular vein are preserved unless the tumor is locally invasive. Transverse incisions are recommended because they provide a better cosmetic result and heal faster than vertical incisions.

If the voice is normal (and vocal cords moved normally before the operation) and the recurrent laryngeal nerve is found to be surrounded by tumor at operation, the nerve usually can be dissected free from the tumor with preservation of function. This is best accomplished by identifying the nerve caudad to the tumor. Lymph nodes that frequently extend into the anterior superior mediastinum usually can be removed via the cervical incision, as indicated by the experimental studies of Chouke and co-workers.[40] They observed a lack of communication between lymphatic channels in the anterior or superior mediastinum and those in more inferior mediastinal levels.

In cases of medullary thyroid cancer, prophylactic neck dissections and, frequently, standard radical neck dissections are recommended. Some patients who have had total thyroidectomies for medullary cancer, but who have no clinical evidence of metastasis, may be evaluated for residual tumors by provocative tests (calcium or pentagastrin infusion) to determine if calcitonin levels have increased.[41-43] If residual medullary cancer is present, serum and urine calcitonin levels will increase in response to infusion of calcium or pentagastrin.[42,43]

Postoperative Management

Following total thyroidectomy for papillary and follicular cancer, the patient is usually given a dosage of 25 μg of liothyronine sodium (Cytomel) orally three times a day. After three months, when the patient has been reassured and his surgical wound is completely healed, this medication is discontinued for two weeks and the patient is given a scanning dose (1 mCi) of iodine 131. Liothyronine (triiodothyronine or T_3) is used postoperatively for thyroid hormone replacement rather than thyroxine (T_4) because it has a half-life of about a day, whereas T_4 has a half-life of about a week. Thus, one can be assured that by two weeks after discontinuing T_3, serum thyroid-stimulating hormone (TSH) levels will be substantially elevated. If there is no radioactive iodine uptake in the neck or elsewhere in the body, the patient's medication is changed to about 0.2 mg of levothyroxine sodium per day. Serum thyroglobulin determination is a useful marker for metastatic differentiated thyroid cancer and is most sensitive when the patient is hypothyroid, that is, just before his scan, because a TSH test is an excellent provocative test for thyroglobulin.[44,45] If the thyroglobulin is positive, then persistent disease should be suspected.[46] If negative, persistent or recurrent tumor is less likely.

If there is uptake of radioactive iodine in the lateral portion of the neck suggesting nodal metastasis, this area should be carefully examined. If lymph nodes are palpable, a modified radical neck dissection should be done. If no nodes are palpable but there is uptake of radioactive iodine, treatment with ^{131}I is recommended. Unfortunately, ^{131}I is not especially effective in treating palpable metastatic nodes but is effective for microscopic functioning metastastic lesions. Wilson and Block[37] reported that treatment with ^{131}I was helpful in only 50 percent of patients with papillary thyroid cancer that metastasized to regional lymph nodes and in none of the patients with follicular carcinoma. External radiation was even less effective in these patients because in all those with either papillary or follicular cancer and nodal involvement tumors recurred. The rates of recurrence in patients similarly treated by a modified neck dissection was 21 percent, and after standard radical neck dissection 29 percent. Although external radiation is generally not effective in treating nodal metastasis, it is useful in patients with metastatic thyroid cancer that does not take up radioactive iodine. It is also useful for treating invasive cancer left in the thyroid bed.[47] Patients treated by thyroidectomy, radioactive iodine and thyroid hormone to suppress TSH, have been reported to have a lower incidence of tumor recurrence.[3]

Prognosis

Thyroid cancer is more lethal than is commonly thought by many clinicians.[48] About 19 percent of 554 treated patients reported by Ibanez and co-workers[49] and 32 percent of 685 patients reported by Woolner and associates died of this disease.[50] Anaplastic thyroid cancer resulted in earlier death due to extensive local and disseminated disease while papillary and follicular cancer were associated with a more protracted course. About a fourth of the latter patients died of local

extension of tumor and the remainder from metastasis to local nodes, lungs, bone and elsewhere.

Suppression of TSH and Adjuvant Therapy

Thyroid hormone should be given for two reasons to all patients who have had thyroid resections for cancer. First, in most cases much of the gland has been removed so thyroid hormone is given to keep the patient euthyroid. Thyroid hormone should also be given to suppress TSH levels. Studies in animals have shown that the development of some forms of thyroid cancer can be prevented by suppressing TSH.[51,52] Several retrospective studies have indicated that recurrence of cancer is minimized and survival dramatically improved in patients treated with exogenous thyroid hormone.[3,37,53,54] We and others[55-57] also have reported that differentiated malignant thyroid tumors have TSH receptors. These tumors also respond metabolically in vitro to TSH stimulation.[55,56,58-60]

The amount of exogenous thyroid hormone required to suppress tumor growth is unknown. Serum TSH levels should be measured periodically to see that they remain suppressed. If there is any question about the proper amount of thyroid hormone, a thyrotropin-releasing hormone (TRH) test may be useful. The lowest dose of thyroid hormone that inhibits the response of serum TSH to TRH should be used.

Chemotherapy is indicated for patients with thyroid cancer that is unresponsive to surgical intervention, TSH suppression or radiation therapy. Generally, these patients have either undifferentiated tumors or recurrent local or disseminated differentiated cancer that has not been successfully treated by an operation and radiation therapy. Approximately 35 percent of patients with uncontrolled thyroid cancer have a partial remission with subjective improvement when treated with doxorubicin hydrochloride (Adriamycin) in a single injected dose of approximately 75 mg per m^2, or divided into three consecutive daily injections that are repeated at three-week intervals. Toxicity may include cardiotoxicity, myelosuppression, leukopenia, thrombocytopenia, alopecia and gastrointestinal problems.[61,62]

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Weight Loss as Determinant of Diuretic Therapy

BODY WEIGHT is the easiest and most accurate way to determine how diuretic therapy is proceeding. . . . Because the fluid from edema can be instantly mobilized into the circulation, if you give a hefty dose of furosemide, and get a prompt diuresis, you will not put the patient into shock. Therefore, the mobilization of this fluid will prevent a catastrophic event.

The problem is that when you see these patients, and they have even massive ascites but very little or no edema—these circumstances are really time bombs. You have to be very careful when you promote a diuresis in these patients. . . . Studies have shown that ascites can be mobilized from the peritoneal cavity at a rate of 900 ml per day. That means you can put the patient in complete shock, but the fluid is going to leave that peritoneal cavity at a maximum rate of 900 ml per day. Therefore, you really have to adjust your diuretic therapy so you do not have the patient losing any more than this amount of fluid per day. If you have ascites plus edema, you should probably aim for a weight loss about 1 kg per day, with diuretics. If there is no edema, you have to be much more careful and you probably have to stay under 0.5 kg of weight loss per day.

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